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PCT

WORLD INTELLECTUAL PROPERTY ORGANIZATION  
International Bureau



INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

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(71) Applicant: SCHERING CORPORATION [US/US]: 2000 Galloping Hill Road, Kenilworth, NJ 07033 (US). (72) Inventors: SPIEGEL, Robert, J. ; 400 Elm Street, Westfield, NJ 07090 (US). CUSS, Francis, M. ; 14 Byron Drive, Basking Ridge, NJ 07920 (US). (74) Agents: HOFFMAN, Thomas, D. et al.: Schering-Plough Corporation, One Girardia Farms, Madison, NJ 07940-1000 (US).		Published <i>With international search report. Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.</i>	
(54) Title: ORAL ADMINISTRATION OF ALPHA INTERFERON TO TREAT LUNG MALIGNANCIES			
(57) Abstract			
<p>A pharmaceutical composition for treating or preventing lung malignancy in mammal comprising recombinant DNA human alpha interferon (rhIFN-<math>\alpha</math>). A use of rhIFN-<math>\alpha</math> for the manufacture of a medicament for treating or preventing a lung malignancy in mammals as well as a method of treating or preventing a lung malignancy in a mammal by administering by oral inhalation to such a mammal afflicted with a lung malignancy an effective amount of rhIFN-<math>\alpha</math> via a nebulizer or metered dose inhaler are disclosed.</p>			

\* See back of page

**+ DESIGNATIONS OF "SU"**

Any designation of "SU" has effect in the Russian Federation. It is not yet known whether any such designation has effect in other States of the former Soviet Union.

**FOR THE PURPOSES OF INFORMATION ONLY**

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

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ORAL ADMINISTRATION OF ALPHA INTERFERON TO  
TREAT LUNG MALIGNANCIES

BACKGROUND OF THE INVENTION

This invention relates to pharmaceutical compositions comprising human alpha interferon (hIFN- $\alpha$ ) as an active ingredient to treat lung malignancies in mammals. The invention also relates to the use of hIFN- $\alpha$  for making medicaments for treating lung malignancies in mammals as well as to methods of treating lung malignancies, generally referred to as lung cancer, by administering by oral inhalation to a mammal in need of such treating an amount of human alpha in recombinant DNA human alpha interferon (rhIFN- $\alpha$ ) effective for such treating.

Human alpha interferon (hIFN- $\alpha$ ) is a naturally occurring mixture of at least eleven compounds including those designated alpha-1 interferon and alpha-2 interferon.

A number of alpha interferon species or components are known and are usually designated by a numeral and letter after the Greek letter alpha. Human alpha-1 interferon is one species contemplated for use in this invention as are the species designated human alpha-2 interferons. Under USAN, recombinant DNA human alpha-2 interferons are designated Interferon Alpha-2a, which can

be made as disclosed in Rubenstein, Biochem. Biophys. Acta (1982), 695, 5-16, and Interferon Alfa-2b. Interferon Alfa-2b is the preferred species for use in this invention and is a recombinant DNA human alpha interferon (hereinafter "rhIFN- $\alpha$ "). Another suitable rhIFN- $\alpha$  included in the scope of this invention is recombinant DNA human interferon alpha-2a.

Human interferon alfa-2b can be produced in bacteria and other microorganisms using recombinant DNA techniques including those disclosed in Nagata et al. Nature, (1980) 284, 316-329; European Patent 32,134 and U.S. Patent No. 4,289,690. Various alpha interferon species are disclosed in U.S. patent 4,503,035.

It is known to administer rhIFN- $\alpha$  parenterally to treat hairy cell leukemia, AIDS-related Kaposi's sarcoma, and hepatitis as well as intralesionally to treat condylomata acuminata. Several groups of investigators have documented that parenterally administered IFN- $\alpha$  does not accumulate in the nasopharyngeal, oropharyngeal, or airway mucosa or in the lung parenchyma in sufficient concentrations or for long enough time periods to be effective against respiratory virus infections.

Recently, it has been shown that non-recombinant human leukocyte alpha-interferon (hereinafter hIFN- $\alpha$ ) can be given to mammals by inhalation to provide high local concentrations in lung and airwayosal tissue. Nebulized hIFN- $\alpha$  inhibits viral ligation in mice (Please give Reference). The t lungs has resulted in measurable serum trations [V. Bocci et al., Antiviral Res. (1984) 211-220].

Intranasally administered rhIFN- $\alpha$  at a dose of units/day prevented rhinovirus transmission

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within families (Douglas, et al, NEJM (1986), Vol. 314, pp65-70. In one Chinese study, interferon- $\alpha$  (hIFN- $\alpha$ ) given both intranasally and intraorally at a dose of 700-1600 units/day was effective in the treatment of influenza, respiratory syncytial viral bronchiolitis, and asthmatic bronchitis (Jia-xiong, et al, Chin Med J. 100:162-166, 1987).

In man, hIFN- $\alpha$  has been inhaled by patients with advanced non-small cell lung cancer at doses up to 120 million International Units ("IU"). Kinnula et al. discloses in the J. Interferon Res. (1989), Vol 9, 419-23 that inhaled hIFN- $\alpha$  resulted in serum concentration and side effects (e.g. fever, headache, influenza-like symptoms and nausea) similar to those disclosed after systemic hIFN- $\alpha$  administration as well as reversible airflow obstruction but no activity against the lung cancer was observed. Inhaled hIFN- $\alpha$  has also been administered to patients suffering from bronchoalveolar carcinoma but no activity on the bronchoalveolar carcinoma has been demonstrated [V. Kinnula et al. J. Interferon Res., (1988) Vol 8, Suppl. 1 p115]

In-vitro activity of rhINF- $\alpha$  A (Roferon) and rhIFN- $\alpha$ D in various human tumor cell assays including lung cancer is known [S.E. Salmon et al., J. Clin. Oncology (1983) Vol. I. p217-225]. Human leukocyte interferon (hIFN- $\alpha$ ) exhibited inhibition of colony formation of greater than 70% against only five including 2 lung tumors of the sixty-two tumor types in an in vitro assay (D.D. Von Hoff et al. Cancer Chemother. Pharmacol. (1982), Vol. 8, 99-103.

#### SUMMARY OF THE INVENTION

The present invention provides a pharmaceutical composition for treating or preventing a lung malignancy in a mammal which composition comprises an effective amount of recombinant DNA human alpha interferon.

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The present invention also provides a use of recombinant DNA human alpha interferon for the manufacture of a medicament for treating or preventing a lung malignancy in a mammal.

This invention also provides a method of treating a lung malignancy in a mammal afflicted with such malignancy which comprises administering via oral inhalation to such a mammal an amount of recombinant human DNA alpha interferon effective for such treating. This invention also provides a method of preventing a lung malignancy in a mammal susceptible to lung malignancy - e.g. heavy smokers of any tobacco products especially cigars and cigarettes, which comprises administering via oral inhalation to such a mammal an amount of recombinant DNA human alpha interferon effective for such preventing.

DETAILED DESCRIPTION OF THE INVENTION

The term "lung malignancy" as used herein means at least one of squamous cell carcinoma, large cell carcinoma, small cell carcinoma, alveolar cell carcinoma, bronchoalveolar carcinoma, adenocarcinoma, bronchogenic carcinoma-in-situ, metastatic carcinoma, or sarcoma from primary tumors outside the lung or airways.

The effectiveness of the interferon therapy of this invention can be shown clinically in mammals, e.g. human beings afflicted with a lung malignancy or susceptible to a lung malignancy due to the smoking tobacco products, especially cigarettes and/or cigars using patients with the following entry criteria:

- (1) a Karnofsky performance status of 60%;
- (2) adequate pulmonary function for undergoing the required inhalation treatment satisfactorily as evidenced by (a) forced expiration volume in one second (FEV<sub>1</sub>) of greater than or equal to 40% and (b) a forced vital capacity (FVC) of greater than or equal to 50% of the

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predicted value and; (3) no serious systemic infections and/or fever.

The recombinant DNA human alpha interferon (rhIFN- $\alpha$ ) administered via oral inhalation in accordance with this invention may be used as monotherapy or as adjunctive therapy with other treatments e.g., chemotherapy or immunotherapy to treat lung malignancy and prevent, inhibit and/or cure the pulmonary metastatic spread of one or more of the types of lung malignancies listed hereinabove. The list of conventional chemotherapeutic agents useful in combination with alpha interferon is disclosed by S. Wadler et al in Cancer Research (1990), Vol 50 pp 5472-3486.

The recombinant DNA human alpha interferon ("rhIFN- $\alpha$ ") is administered by oral inhalation in accordance with this invention as a pharmaceutical composition containing rhIFN- $\alpha$  which may be dissolved or dispersed in a pharmaceutically acceptable carrier suitable for use in a nebulizer and/or a metered dose inhaler. Pharmaceutically acceptable carriers include, for example, water, saline, ethanol and the like which form a rhIFN- $\alpha$  solution or suspension suitable for administration via oral inhalation in accordance with this invention. If desired, the rhIFN- $\alpha$  pharmaceutical composition useful in this invention may also contain minor amounts of non-toxic auxiliary substances such as melting agents, emulsifying agents, preservatives, stabilizers, and pH buffering agents. The preparation of these pharmaceutical compositions is well known to those skilled in the art; see for example Remington's Pharmaceutical Sciences Mack Publishing Co., Easton PA 15th Edition (1975).

A preferred rhIFN- $\alpha$  pharmaceutical composition for use in accordance with this invention is the Intron $\alpha$  A brand of interferon available as a solution from

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Schering-Plough Corporation, Kenilworth, New Jersey. This commercially available Intron A rhIFN- $\alpha$  composition contains glycine, di- and mono- basic sodium phosphate as a buffer and serum albumin. Other preferred rhIFN- $\alpha$  pharmaceutical compositions include any sterile isotonic aqueous solution, e.g. physiological phosphate-buffered saline at pH 7.3 which may also contain pharmaceutically acceptable non-toxic auxiliary agents such as stabilizers and/or surfactants and the desired amount of rhIFN- $\alpha$ . The concentration of rhIFN- $\alpha$  in the pharmaceutical composition may be adjusted by dilution with 0.9% saline solution before administration via oral inhalation. The oral inhalation of drugs by use of nebulizers and metered dose inhalers is well known. See for example Remington, ibid, at chapter 99, pages 1910-1912. Useful nebulizers include the Spira Electro 4 nebulizer, manufactured by Hämeenlinnan Työleskus, Hämeenlinna, Finland, whose use is disclosed by Kinnula et al. in the J. of Interferon Research (1989) Vol. 9 at p420. Useful metered dose inhalers as well as drug delivery systems that help deliver oral aerosolized medications from metered dose inhalers to the lungs include INHAL-AID and INSPIREASE drug delivery systems available from Schering-Plough Corporation, Kenilworth, New Jersey, U.S.A, for as well as those disclosed in the Physicians Desk Reference, 1990 Edition, for use with bronchodilators. The output of the nebulizer or metered dose inhaler for use in this invention should consistently and reliably produce particles and/or droplets having a mass median aerodynamic diameter (M.M.A.D.) above about 0.5 microns, preferably having a M.M.A.D. above about 0.5 and less than about 8 microns and more preferably having a M.M.A.D. above about 0.5 to about 5.0 microns. Orally inhaled particles and/or droplets containing rhIFN- $\alpha$  having a M.M.A.D in the range of above about 0.5 to less than

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about 8 microns are suitable for deposition on the peripheral airways and lungs and thus maximize the beneficial effects of inhaled rhIFN- $\alpha$ . Droplets and particles having a M.M.A.D. greater than 8 microns become impacted in the upper airways; and those having a M.M.A.D. less than about 0.5 microns tend to behave like a gas and are exhaled. However, droplets and/or particles of rhIFN- $\alpha$  having the preferred M.M.A.D. have a high surface energy and tend to agglomerate. The addition of a surfactant preferably a non-volatile liquid soluble in the propellant used in nebulizers or metered dose inhalers is desirable to lessen such agglomeration.

The effective amount of rhIFN- $\alpha$  for treating and/or preventing a lung malignancy in accordance with this invention is a dosage range of rhIFN- $\alpha$  of about  $1 \times 10^6$  international units (IU) to about  $1 \times 10^{11}$  IU, preferably about  $1 \times 10^6$  IU to about  $5 \times 10^{10}$  IU, and more preferably about  $1 \times 10^6$  IU to about  $2 \times 10^{10}$  IU. The rhIFN- $\alpha$  maybe administered daily in single or divided doses.

Based on the judgment of the attending clinician, the amount of rhIFN- $\alpha$  administered and the treatment regimen used will, of course, be dependent on the age, sex and medical history of the patient being treated, the severity of the specific lung malignancy and the tolerance of patient to the treatment regimen as evidenced by local toxicity (e.g. nasal irritation and/or bleeding) and by systemic side effects (e.g. fever, malaise, pancytopenia, CNS depression, gastrointestinal irritation and elevated liver enzymes).

The following is a description of the clinical protocol to be utilized for treating and preventing lung malignancies.

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#### Study Design

Prior to enrollment, all patients are thoroughly examined and their disease clinically staged using chest x-rays, computerized tomography, EKG, hematologic and blood chemistries. Clotting studies including total fibrinogen determination, PTT, PT, TT, and fibrin degradation products are conducted. Karnofsky performance status, pulmonary function including peak expiratory flow (PEF), forced expiratory volume in one second (FEV<sub>1</sub>), and forced vital capacity (FVC) are measured. Subjective and objective symptoms including the number and severity of coughing bouts, shortness of breath, pain and coughing-up of blood as well as body temperature, blood pressure, and heart rate are measured.

#### Serum rhIFN- $\alpha$ Concentrations

Serum rhIFN- $\alpha$  concentrations are determined by use of commercially available immunoradiometric assays (Abbott Diagnostics and Centocor, respectively) or by vesicular stomatitis virus (VSV) plaque reduction in HEp2 cultures. Measurement are performed before inhalation and 2hr, 5hr, 10hr, 15hr and 24 hr after inhalation.

#### Toxicity Evaluation and Response Criteria

Each patient is vigorously monitored for early signs of toxicity as well as radiographic evidence of clinical effectiveness throughout the treatment course and on a regular basis thereafter. Methods of evaluation include frequent physician examination, a regular schedule for performance of laboratory procedures including hematologic and serum chemistries pulmonary function and clotting studies. Radiographic studies include chest x-rays and CT scans as appropriate. Toxicity is graded in accordance with the Work Health Organization's recommendations for grading of acute and

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subacute toxicity. Performance status is graded from zero to four with complete disability being defined as four. Tumor response is determined by means of serial radiographic studies. Areas of referenced tumors are determined by multiplication of the longest diameter by the greatest perpendicular diameter. Complete response would be then defined as the disappearance of all measurable disease determined by observation separated by at least four weeks with the appearance of no new lesions within the radiation portal. Partial response is a 50% decrease in the referenced tumor mass and stable disease would be defined as a less than 50% decrease in tumor size, or less than 25% increase. A tumor growth larger than 25% is considered progressive disease.

Other response criteria include relief of subjective and objective symptoms especially a significant reduction in (1) the number and severity of coughing bouts (2) the shortness of breath, and (3) coughing-up of blood. Weight gain, increase in pulmonary capacity, exercise capacity and reduction in adjunctive or concomitant cancer therapies would also indicate effective treatment.

Symptoms and objective side effects of rhIFN- $\alpha$  therapy including changes in body temperature, airflow obstruction and flu-like symptom are also measured.

A reduction in tumor growth and/or lung malignancy by administering by oral inhalation rhIFN- $\alpha$  to patients in need of such administer is expected.

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WHAT IS CLAIMED IS:

1. A pharmaceutical composition for treating or preventing a lung malignancy in a mammal which composition comprises an effective amount of recombinant DNA human alpha interferon.
2. A use of recombinant DNA human alpha interferon for the manufacture of a medicament for treating or preventing a lung malignancy in a mammal.
3. A method of treating a lung malignancy in a mammal afflicted with a lung malignancy which comprises administering by oral inhalation to such a mammal an amount of recombinant DNA human alpha interferon effective for such treating.
4. A method of preventing a lung malignancy in a mammal susceptible to a lung malignancy which comprises administering by oral inhalation to such a mammal an amount of recombinant DNA human alpha interferon effective for such preventing.
5. A pharmaceutical composition or a use or method of any preceding claim wherein the lung malignancy is selected from the group of squamous cell carcinoma, large cell carcinoma, small cell carcinoma, alveolar cell carcinoma, bronchoalveolar carcinoma, adenocarcinoma, bronchogenic carcinoma-in-situ, metastatic carcinoma or sarcoma from primary tumors outside the lung or airways.
6. A pharmaceutical composition or use or method of treating or preventing of any preceding claim wherein the

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recombinant DNA human alpha interferon is administered by a nebulizer.

7. A pharmaceutical composition or a use or a method of treating or preventing any of the preceding claims wherein the recombinant DNA human alpha interferon is administered by a metered dose inhaler.

8. A pharmaceutical composition or a use or method of treating or preventing any of the preceding claims wherein the recombinant human DNA alpha interferon is interferon alpha-2a.

9. A pharmaceutical composition or a use or method of treating or preventing any of the preceding claims wherein the recombinant human DNA alpha interferon is interferon alpha-2b.

10. A pharmaceutical composition or a use or method of treating or preventing any of the preceding claims where the amount of recombinant human DNA alpha interferon is in the range of about  $1 \times 10^6$  IU to about  $1 \times 10^{11}$  IU.

11. A pharmaceutical composition or a use or method of any of the preceding claim wherein the output of the nebulizer metered dose inhaler is in the form of particles of an aqueous solution of recombinant human alpha interferon having a mass median aerodynamic diameter of above about 0.5 to about 5.0 microns.

# INTERNATIONAL SEARCH REPORT

International Application No. PCT/US 91/09084

## I. CLASSIFICATION OF SUBJECT MATTER (If several classification symbols apply, indicate all)<sup>6</sup>

According to International Patent Classification (IPC) or to both National Classification and IPC  
IPC5: A 61 K 37/66

## II. FIELDS SEARCHED

Minimum Documentation Searched<sup>7</sup>

Classification System	Classification Symbols
IPC5	A 61 K

Documentation Searched other than Minimum Documentation  
to the Extent that such Documents are Included in Fields Searched<sup>8</sup>

## III. DOCUMENTS CONSIDERED TO BE RELEVANT<sup>9</sup>

Category	Citation of Document, <sup>11</sup> with indication, where appropriate, of the relevant passages <sup>12</sup>	Relevant to Claim No. <sup>13</sup>
X	Dialog Information Services, file 155, Medline 66-92, Dialog Acc.No. 07026016, Medline Acc.No. 89328016, Kinnula V. et al: "Pharmacokinetics and toxicity of inhaled human interferon-alpha in patients with lung cancer", J Interferon Res Aug 1989, 9 (4) p 419-23	1-2, 5-11
Y	---	6-7, 11
X	Dialog Information Services, file 155, Medline 66-92, Dialog Acc.No. 07459116, Medline Acc.No. 90366116, Kinnula V. et al: "Effect of inhaled natural interferon-alpha on diffuse bronchioalveolar carcinoma", Eur J Cancer 1990, 26 (6) p740-1	1-2, 5-11
Y	---	6-7, 11

### \* Special categories of cited documents:<sup>10</sup>

- "A" document defining the general state of the art which is not considered to be of particular relevance
- "E" earlier document but published on or after the international filing date
- "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- "O" document referring to an oral disclosure, use, exhibition or other means
- "P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance, the claimed invention cannot be considered novel or cannot be considered to involve an inventive step

"Y" document of particular relevance, the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"Z" document member of the same patent family

## IV. CERTIFICATION

Date of the Actual Completion of the International Search

9th April 1992

Date of Mailing of this International Search Report

28 APR 1992

International Searching Authority

EUROPEAN PATENT OFFICE

Signature of Authorized Officer

Mme N. KUIPER

III. DOCUMENTS CONSIDERED TO BE RELEVANT		(CONTINUED FROM THE SECOND SHEET)
Category	Citation of Document, with indication, where appropriate, of the relevant passages	Relevant to Claim No
X	Dialog Information Services, file 155, Medline 66-92, Dialog Acc.No. 06185262, Medline Acc.No. 87159262, Fidler I.J. et al: "Direct antiproliferative effects of recombinant human interferon-alpha B/D hybride on human tumor cell line", Cancer Res Apr 15 1987, 47 (8) p2020-7	1-2,5,8-9
Y	---	6-7, 11
X	Dialog Information Services, file 155, Medline 66-92, Dialog Acc.No. 05998255, Medline Acc.No. 86299255, Ravine T.J. et al: "Treatment with human recombinant leukocyte interferons inhibits in vitro invasive ability of human lung carcinoma cells", Clin Exp Metastasis Jul-Sep 1986, 4 (3) p191-203	1-2,5,8-9
Y	---	6-7, 11
X	Dialog Information Services, file 155, Medline 66-92, Dialog Acc.No. 07147980, Medline Acc.No. 90054980, Kardamakis D. et al: "Recombinant human interferon alpha-2b enhances the radiosensitivity of small cell lung cancer in vitro", Anticancer Res Jul-Aug 1989, 9 (4) p1041-4	1-2,5,8-9
Y	---	6-7, 11
X	Dialog Information Services, file 155, Medline 66-92, Dialog Acc.No. 05666357, Medline Acc.No. 85282357, Grunberg S.M. et al: "Phase II study of recombinant alpha interferon in the treatment of advanced non-small cell lung carcinoma", Cancer Treat Rep Sep 1985, 69 (9). p1031-2	1-2,5,8-9
Y	---	6-7, 11
X	Dialog Information Services, file 155, Medline 66-92, Dialog Acc.No. 04920443, Medline Acc.No. 83153443, Jones D.H. et al: "Human lymphoblastoid interferon in the treatment of small cell lung cancer", Br J cancer Mar 1983, 47 (3) p361-6	1-2,5,8-10
Y	---	6-7, 11

<b>III. DOCUMENTS CONSIDERED TO BE RELEVANT</b>		<b>(CONTINUED FROM THE SECOND SHEET)</b>
<b>Category</b>	<b>Citation of Document, with indication, where appropriate, of the relevant passages</b>	<b>Relevant to Claim No</b>
X	EP, A1, 0372809 (SCHERING CORPORATION) 13 June 1990, see the whole document	1-2,5,8- 10
Y		6-7, 11
	---	
X	EP, A1, 0077063 (VIRAL GENETICS, INC.) 20 April 1983, see the whole document	1-2,5,8- 10
Y		6-7, 11
	---	
X	Derwent's abstract, No. 88-262 741/37, SU 1 377 113, publ. week 8837 KIEV MED INST	1-2,8-9
Y		6-7, 11
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## FURTHER INFORMATION CONTINUED FROM THE SECOND SHEET

V.  OBSERVATIONS WHERE CERTAIN CLAIMS WERE FOUND UNSEARCHABLE<sup>1</sup>

This international search report has not been established in respect of certain claims under Article 17(2) (a) for the following reasons:

1.  Claim numbers.....\*), because they relate to subject matter not required to be searched by this Authority, namely:

\* )3-4 and partially 5-11.

Methods for treatment of the human or animal body by surgery or therapy, as well as diagnostic methods. See PCT Rule 39.1(iv).

2.  Claim numbers 1-5, because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

The wording "lung malignancy" is too broadly formulated to permit a meaningful search.

The search on claims 1-5 has therefore been incomplete. (See Art 6).

3.  Claim numbers....., because they are dependent claims and are not drafted in accordance with the second and third sentences of PCT Rule 8.4(a).

VI.  OBSERVATIONS WHERE UNITY OF INVENTION IS LACKING<sup>2</sup>

This International Searching Authority found multiple inventions in this international application as follows:

1.  As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims of the international application.

2.  As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims of the international application for which fees were paid, specifically claims:

3.  No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the the claims. It is covered by claim numbers:

4.  As all searchable claims could be searched without effort justifying an additional fee, the International Searching Authority did not invite payment of any additional fee.

## Remark on Protest

The additional search fees were accompanied by applicant's protest.  
 No protest accompanied the payment of additional search fees.

ANNEX TO THE INTERNATIONAL SEARCH REPORT  
ON INTERNATIONAL PATENT APPLICATION NO.PCT/US 91/09084

SA 54926

This annex lists the patent family members relating to the patent documents cited in the above-mentioned international search report.  
The members are as contained in the European Patent Office EDP file on 28/02/92.  
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Patent document cited in search report	Publication date	Patent family member(s)	Publication date
EP-A1- 0372809	13/06/90	AU-D- 4802590 CA-A- 2004202 EP-A- 0446279 WO-A- 90/06135	26/06/90 01/06/90 18/09/91 14/06/90
EP-A1- 0077063	20/04/83	CA-A- 1190148 DE-A- 3278234 EP-A- 0305551 JP-A- 58077824 JP-B- 63065050 US-A- 4507281 US-A- 4957734	09/07/85 21/04/88 08/03/89 11/05/83 14/12/88 26/03/85 18/09/90

For more details about this annex : see Official Journal of the European Patent Office, No. 12/82

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